AMENDMENTS TO THE CLAIMS

Please amend claims 1, 11, 25, 41, and 45, as set forth below.

Please cancel claims 2, 15, 18-24, 26, 42, 43, and 47-52, without prejudice or disclaimer.

The current listing of claims replaces all prior listings.

1. (Currently amended) A method of generating a humanized mouse comprising recombining a first DNA construct with a second DNA construct,

wherein the first DNA construct has a mouse DNA sequence contained therein, and wherein the second DNA construct has a human DNA sequence contained therein, wherein the first and second constructs have the same order and organization relative to the human DNA sequences when present in the genome of a human;

a) generating at least two recombinant chimeric DNA constructs comprising human and mouse DNA sequences of the first and second DNA constructs, wherein each chimeric DNA construct comprises human DNA at one end of the chimeric DNA construct and mouse DNA at the other end of the chimeric DNA construct, and wherein a first chimeric DNA construct of the at least two recombinant chimeric DNA constructs comprises 5' regulatory DNA sequences and a second chimeric DNA construct of the at least two recombinant chimeric DNA constructs comprises 3' regulatory DNA sequences;

b) ligating ~~the end of~~ the human DNA ends of the first and second ~~comprising the at least two~~ chimeric DNA constructs, thereby allowing for modification of human DNA of the ligated chimeric DNA constructs;

c) recombining the ligated chimeric DNA constructs of step (b) with the second DNA construct to produce a third DNA construct, wherein the third DNA construct comprises human sequences of the second DNA construct flanked by mouse sequences of the first DNA construct;

d) introducing the third DNA construct into a mouse embryogenic stem cell;

e) introducing the embryogenic stem cell of step (d) into an mouse blastocyst, thereby producing a chimeric blastocyst; and

f) implanting the chimeric blastocyst into a pseudopregnant mouse, wherein the pseudopregnant mouse delivers a humanized mouse, thereby generating a humanized mouse.

2. (Canceled)

3. (Original) The method of claim 1, wherein the first DNA construct is a bacterial artificial chromosome.

4. (Original) The method of claim 1, wherein the second DNA construct is a bacterial artificial chromosome.

5. (Original) The method of claim 4, wherein the bacterial artificial chromosome is linearized.

6. (Original) The method of claim 1, wherein the recombining is carried out in a strain of *E. coli*.

7. (Previously presented) The method of claim 6, wherein the *E. coli* is deficient for *sbcB*, *sbcC*, *recB*, *recC* or *recD* activity and has a temperature sensitive mutation in *recA*.

8. (Previously presented) The method of claim 1, wherein the human DNA sequence is selected from the group consisting of a G-protein coupled receptor gene, a kinase gene, a phosphatase gene, an ion channel gene, a nuclear receptor gene, an oncogene, a cancer suppressor gene, a viral receptor gene, a bacterial receptor gene, a P450 gene, an insulin receptor gene, an immunoglobin gene, a metabolic pathway gene, a transcription factor gene, a cytokine gene, a cell signaling pathway gene and a cell cycle gene.

9. (Original) The method of claim 1, wherein the third DNA construct is a bacterial artificial chromosome.

10. (Original) The method of claim 1, wherein the human DNA sequence is a human gene sequence having at least one intron contained therein.

11. (Currently amended) The method of claim 10, wherein the third DNA construct has a selection marker contained within the at least one intron of the human DNA sequence.

12. (Original) The method of claim 11, wherein the selection marker is added following the recombining step.

13. (Original) The method of claim 11, wherein the selection marker is a positive selection marker.

14. (Previously amended) The method of claim 11, wherein the third DNA construct has a second selection marker that flanks the first or the second mouse DNA sequence.

15. (Canceled)

16. (Previously presented) The method of claim 1, wherein the human DNA sequence of the first DNA chimeric construct comprises a coding sequence comprising a start codon having a 5' end, and wherein the mouse DNA sequence of the first chimeric DNA construct is joined to the human DNA coding sequence at the 5' end of the start codon.

17. (Previously presented) The method of claim 16, wherein the human DNA sequence of the second chimeric DNA construct comprises a coding sequence comprising a stop codon having a 3' end, and wherein the mouse DNA sequence of the second chimeric DNA construct is joined to the human DNA coding sequence at the 3' end of the stop codon.

18-24. (Canceled)

25. (Currently amended) A method for generating a DNA construct for performing homologous recombination within a cell by

recombining a first DNA construct with a second DNA construct, wherein the first DNA construct has a non-human animal DNA sequence contained therein,
wherein the second DNA construct has a human DNA sequence contained therein,
wherein the first and second construct have the same order and orientation relative to the human DNA sequences present in the genome of a human;

a) generating at least two recombinant chimeric DNA constructs comprising human and non-human animal DNA sequences of the first and second DNA constructs, wherein each

chimeric DNA construct comprises human DNA at one end of the chimeric DNA construct and non-human animal DNA at the other end of the chimeric DNA construct, and wherein a first chimeric DNA construct of the at least two recombinant chimeric DNA constructs comprises 5' regulatory DNA sequences and a second chimeric DNA construct of the at least two recombinant chimeric DNA constructs comprises 3' regulatory DNA sequences;

b) ligating ~~the end of~~ the human DNA ends of the first and second ~~comprising the at least two~~ chimeric DNA constructs, thereby allowing for modification of human DNA of the ligated chimeric DNA constructs;

c) recombining the ligated chimeric DNA constructs of step (b) with the second DNA construct to produce a third DNA construct, wherein the third DNA construct comprises human sequences of the second DNA construct flanked by non-human animal sequences of the first DNA construct; and

d) isolating the recombined third DNA construct of step (c).

26. (Canceled)

27. (Original) The method of claim 25, wherein the first DNA construct is a bacterial artificial chromosome.

28. (Original) The method of claim 25, wherein the second DNA construct is a bacterial artificial chromosome.

29. (Original) The method of claim 28, wherein the bacterial artificial chromosome is linearized.

30. (Original) The method of claim 25, wherein the recombining is carried out in a strain of *E. coli*.

31. (Original) The method of claim 25, wherein the *E. coli* is deficient for *sbcB*, *sbcC*, *recB*, *recC* or *recD* activity and has a temperature sensitive mutation in *recA*.

32. (Previously presented) The method of claim 25, wherein the human DNA sequence is selected from the group consisting of a G-protein coupled receptor gene, a kinase gene, a phosphatase gene, an ion channel gene, a nuclear receptor gene, an oncogene, a cancer

suppressor gene, a viral receptor, a bacterial receptor gene, a P450 gene, an insulin receptor gene, an immunoglobin gene, a metabolic pathway gene, a transcription factor gene, a cytokine gene, a cell signaling pathway gene and a cell cycle gene.

33. (Original) The method of claim 25, wherein the third DNA construct is a bacterial artificial chromosome.

34. (Original) The method of claim 25, wherein the human DNA sequence is a human gene sequence having at least one intron contained therein.

35. (Previously presented) The method of claim 34, wherein the third DNA construct has a selection marker contained within the at least one intron.

36. (Original) The method of claim 35, wherein the selection marker is added following the recombining step.

37. (Original) The method of claim 35, wherein the selection marker is a positive selection marker.

38. (Previously presented) The method of claim 35, wherein the third DNA construct has a second selection marker that flanks the first or the second non-human animal DNA sequence.

39. (Previously presented) The method of claim 25, wherein the human DNA sequence of the first DNA chimeric construct comprises a coding sequence comprising a start codon having a 5' end, and wherein the first non-human DNA sequence the first chimeric construct is joined to the human DNA coding sequence at the 5' end of the start codon.

40. (Previously presented) The method of claim 39, wherein the human DNA sequence of the second chimeric DNA construct comprises a coding sequence comprising a stop codon having a 3' end, and wherein the non-human DNA sequence of the second chimeric DNA construct is joined to the 3' of the stop codon.

41. (Currently amended) A humanized mouse produced by the method of claim 11, wherein the human DNA sequence is a gene selected from a G-protein coupled receptor gene, a kinase gene, a phosphatase gene, an ion channel gene, a nuclear receptor gene, an oncogene, a cancer

suppressor gene, a viral receptor gene, a bacterial receptor gene, a P450 gene, an insulin receptor gene, an immunoglobin gene, a transcription factor gene, a cytokine gene and a cell cycle gene, wherein the mouse comprises a selection marker contained within the at least one intron, and wherein the mouse is homozygous for the human DNA gene.

Claim 42-43. (Canceled)

44. (Previously presented) The humanized mouse of claim 41, wherein the gene is a PXR, RXR, CYP3A4, CYP2B6, CYP2C9 or MDR1 gene.

45. (Currently amended) A method of generating a humanized cell, comprising:

recombining a first DNA construct with a second DNA construct,

wherein the first DNA construct has a non-human animal DNA sequence contained therein, and

wherein the second DNA construct has a human DNA sequence contained therein,

wherein the first and second constructs have the same order and orientation relative to the human DNA sequences when present in the genome of a human;

a) generating at least two recombinant chimeric DNA constructs comprising human and non-human animal DNA sequences of the first and second DNA constructs, wherein each chimeric DNA construct comprises human DNA at one end of the chimeric DNA construct and non-human animal DNA at the other end of the chimeric DNA construct, and wherein a first chimeric DNA construct of the at least two recombinant chimeric DNA constructs comprises 5' regulatory DNA sequences and a second chimeric DNA construct of the at least two recombinant chimeric DNA constructs comprises 3' regulatory DNA sequences;

b) ligating ~~the end of~~ the human DNA ends of the first and second ~~comprising the at least two~~ chimeric DNA constructs, thereby allowing for modification of human DNA of the ligated chimeric DNA constructs;

c) recombining the ligated chimeric DNA constructs of step (b) with the second DNA construct to produce a third DNA construct, wherein the third DNA construct comprises human

sequences of the second DNA construct flanked by non-human animal sequences of the first DNA construct; and

d) introducing the recombined third DNA construct into a non-human animal cell of the same species as the non-human animal DNA sequences of the first construct, thereby generating a humanized cell.

46. (Previously presented) The method of claim 45, wherein the non-human animal cell is a mouse embryogenic stem cell.

47-52. (Canceled)